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Opinions

Nonalcoholic fatty liver disease: A risk factor for chronic kidney disease

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Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, affecting approximately one-third of the population. Its prevalence is estimated to be 24% in Latin America, reaching 68% in specific groups such as individuals with type 2 diabetes (T2DM) [1].

The prevalence of NAFLD has increased in parallel with the prevalence of obesity, T2DM and metabolic syndrome (MS) worldwide. This is primarily due to lifestyle changes, which have led to a subsequent rise in morbidity and mortality caused by hepatic and cardiovascular diseases. MS, which encompasses obesity, systemic arterial hypertension (SAH), and T2DM, is widely recognized as a significant risk factor for multiorgan damage, including involvement of cardiovascular and renal system [2].

Recent studies have estimated that 20%–25% of individuals with NAFLD also have chronic kidney disease (CKD) and share common risk factors with obesity, T2DM, SAH and MS. However, the independent role of NAFLD in the development of CKD, which defined as a glomerular filtration rate of <60 mL/min/1.73 m, remains under discussion, and will be the focus of this paper [3,4].

Renal alterations resulting from obesity, SAH and T2DM are well known. Obesity is an independent risk factor for CKD and is associated with proteinuria and pathological findings such as podocyte hypertrophy and focal segmental glomerular sclerosis, even in the absence of SAH. It also contributes to CKD by increasing pressure transmitted to intraglomerular capillaries, leading to glomerulosclerosis and loss of renal function. Therefore, SAH and T2DM represent confounding factors in the evaluation of a patient with NAFLD who develops CKD [5,6].

Sinn *et al.* [7] conducted a retrospective cohort study involving 41,430 individuals without CKD and observed that CKD occurred more frequently in individuals with NAFLD than in those without NAFLD. This association remained even after adjusting for traditional risk factors and potential metabolic mediators. Moreover, the association between NAFLD and incident CKD was found to be stronger in participants with liver fibrosis than in those without. Based on these findings the authors hypothesized that NAFLD with fibrosis may be an independent risk factor for the development of CKD.

The pathogenesis of NAFLD is multifactorial and encompasses genetic and environmental factors, as well as insulin resistance, oxidative stress and intestinal dysbiosis. The pathogenic mechanisms affecting NAFLD and CKD development are not well understood, however, these various factors may contribute to the association of both diseases [2,6,8].

A genetics study conducted on NAFLD demonstrated that the PNPLA3 gene variant (patatin-like phospholipase domain-containing 3 gene) is an independent risk factor for NAFLD but also for severe liver diseases within the NAFLD spectrum, such as nonalcoholic steatohepatitisn (NASH), cirrhosis, and HCC. Recent data have shown an association between the development of CKD in children and adults with NAFLD, regardless of the presence of traditional risk factors for CKD and severity of NAFLD. This association is particularly observed in individuals which carry the PNPLA3 gene variant (PNPLA3/148 M rs738409) [9].

The influence of oxidative stress on the development of CKD in patients with NAFLD has also been a topic of discussion. Oxidative stress and cellular aging are believed to play a role as potential mediators in the pathogenesis of both diseases. The presence of increased visceral adiposity leads to the production of reactive oxygen species, which in turn reduces the antioxidant capacity within the body. This alteration in the inflammatory cascade impacts adipocytes in the liver and kidneys and is significantly associated with organ dysfunction [10].

In recent years, there has been growing evidence implicating intestinal dysbiosis in the pathogenesis of NAFLD and CKD. Alterations in the composition of intestinal bacteria can disrupt proinflammatory and

Abbreviation: NAFLD, Nonalcoholic Fatty Liver Disease; NASH, Nonalcoholic Steatohepatitis; CKD, Chronic Kidney Disease; T2DM, Type 2 diabetes; SAH, Systemic Arterial Hypertension; MS, Metabolic Syndrome; PNPLA3, Protein containing the patatin-like phospholipase domain

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metabolic mechanisms, resulting in the production of toxins that can cause damage to the liver and kidneys [11].

Liver fibrosis has also been recognized as a predisposing factor for the development of CKD in patients with NAFLD. Several studies have shown an association between a more advanced degree of hepatic fibrosis and a higher prevalence of CKD [12,13]. Musso G. *et al.* (8) conducted a meta-analysis to investigate the association between the severity of NAFLD and the presence and severity of CKD. They analyzed 33 studies (63,902 participants) and found that NAFLD was associated with an increased risk of prevalent CKD and incident. NASH was associated with a higher prevalence and incidence of CKD compared to simple steatosis. However, the authors admitted the limitations of the included studies, such as the small size of studies utilizing liver histology and the suboptimal sensitivity of ultrasound and biochemistry for NAFLD detection in population-based studies.

Considering the wide range of histological changes seen in NAFLD, monitoring strategies for individuals with this condition aim to identify patients with a liver fibrosis of ≥2. While there is no definitive consensus in the literature regarding the optimal method to identify these patients, a combined assessment utilizing noninvasive marker such as the FIB-4 score and/or transient hepatic elastography can help to reduce the misclassification of liver fibrosis [14].

At the present time, establishing a causal relationship between NAFLD and CKD can be challenging due to the presence of overlapping metabolic disorders in affected individuals. It remains unclear whether there is a direct causal link between NAFLD and CKD or if they share common underling mechanisms, such as metabolic syndrome, oxidative stress, and genetic predisposition. Further research is needed to elucidate the nature of their relationship and determine the extent of shared mechanisms between the two conditions.

In conclusion, NAFLD and CKD are significant public health concerns worldwide, and recent evidence indicates a strong association between the two diseases, independent of other confounding conditions like obesity, arterial hypertension, T2DM and MS. Epidemiological findings suggest that NAFLD acts as an independent risk factor for the development of CKD. However, further studies are required to confirm these hypotheses. It is also essential to investigate the potential impact of NAFLD fibrosis, intestinal dysbiosis, and genetic polymorphisms on the development of CKD in patients with NAFLD.

Declaration of interests

None.

References

[1] Rojas YAO, Cuellar CLV, Barrón KMA, Arab JP, Miranda AL. Non-alcoholic fatty liver disease prevalence in Latin America: a systematic review and meta-analysis. Ann Hepatol 2022;27(6):100706. https://doi.org/10.1016/j.aohep.2022.100706.
[2] Rinaldi L, Pafundi PC, Galiero R, Caturano A, Morone MV, Silvestri C, et al. Mechanisms of non-alcoholic fatty liver disease in the metabolic syndrome. A narrative review. Antioxidants (Basel) 2021;10(2):270. https://doi.org/10.3390/antiox10020270.
[3] Targher G, Byrne CD. Non-alcoholic fatty liver disease: an emerging driving force in chronic kidney disease. Nat Rev Nephrol [Internet] 2017;13(5):297–310. https://doi.org/10.1038/nrneph.2017.16.
[4] Levey AS, Eckardt KU, Dorman NM, Christiansen SL, Cheung M, Jadoul M, et al. Nomenclature for kidney function and disease: executive summary and glossary from a kidney disease: improving Global Outcomes consensus conference. Kidney Int 2020;97(6):1117–29. https://doi.org/10.1016/j.kint.2020.02.010.
[5] Akahane T, Akahane M, Namisaki T, Kaji K, Moriya K, Kawaratani H, et al. Association between non-alcoholic fatty liver disease and chronic kidney disease: a cross-sectional study. J Clin Med 2020;28(6):1635. 9. https://doi.org/10.3390/jcm9061635.
[6] Byrne CD, Targher G. NAFLD as a driver of chronic kidney disease. J Hepatol [Internet] 2020;72(4):785–801. https://doi.org/10.1016/j.jhep.2020.01.013.
[7] Sinn DH, Kang D, Jang HR, Gu S, Cho SJ, Paik SW, et al. Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: a cohort study. J Hepatol 2017;67(6):1274–80. https://doi.org/10.1016/j.jhep.2017.08.024.
[8] Musso G, Cassader M, Cohney S, Pinach S, Saba F, Gambino R. Emerging liver-kidney interactions in nonalcoholic fatty liver disease. Trends Mol Med 2015;21(10):645–62. https://doi.org/10.1016/j.molmed.2015.08.005.
[9] Mantovani A, Taliento A, Zusi C, Baselli G, Prati D, Granata S, Zaza G, et al. PNPLA3 I148M gene variant and chronic kidney disease in type 2 diabetic patients with NAFLD: clinical and experimental findings. Liver Int 2020;40(5):1130–41. https://doi.org/10.1111/liv.14419.
[10] García-Ruiz C, Fernández-Checa JC. Mitochondrial oxidative stress and antioxidants balance in fatty liver disease. Hepatol Commun 2018;30(12):1425–39 2. https://doi.org/10.1002/hep4.1271.
[11] Truong E, Noureddin M. The interplay between nonalcoholic fatty liver disease and kidney disease. Clin Liver Dis 2022;26(2):213–27. https://doi.org/10.1016/j.cld.2022.01.008.
[12] Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ, et al. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7(10):1104–12. https://doi.org/10.1016/j.cgh.2009.05.033.
[13] Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61(5):1547–54. https://doi.org/10.1002/hep.27368.
[14] Ciardullo S, Ballabeni C, Trevisan R, Perseghin G. Liver stiffness, albuminuria, and chronic kidney disease in patients with NAFLD: a systematic review and meta-analysis. Biomolecules 2022;12(1):105. https://doi.org/10.3390/biom12010105.